R9 ISOLATION PROCEDURE, SPECIES IDENTIFICATION AND CLINICAL SIGNIFICANCE OF ASPERGILLUS SPP., *SCEDOSPORIUM* SPP., AND OTHER FILAMENTOUS FUNGI IN CYSTIC FIBROSIS

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Aspergillus fumigatus is the most common agent associated of airways colonization in CF, it may cause various diseases including asthma, bronchitis and aspergilloma, as well as invasive aspergillosis after lung transplantation. The most relevant clinical form in CF patients remains allergic broncho-pulmonary aspergillosis (ABPA). Other filamentous fungi are increasingly reported in CF, such as *Scedosporium apiospermum* and some *Aspergillus* spp., particularly *Aspergillus flavus, Aspergillus terreus, Aspergillus niger* and *Aspergillus nidulans* which may be found transiently. *Scedosporium apiospermum* is now recognized as an important colonizer of the airways in CF patients, but little is known about the prevalence of non-*fumigatus Aspergillus* species. Some of these fungi may be responsible for allergic broncho-pulmonary disease similar to ABPA. The microbiological diagnosis usually relies on direct microscopic examination and culture of CF sputum samples. However, at present, there is no standardization of mycological examination of CF samples, the culture media used, as well as temperature or incubation times. The absence of selective media, as an insufficient incubation time, may hamper the recovery of some species like *Scedosporium apiospermum* which is usually associated to the more rapidly growing fungus *Aspergillus fumigatus*.
Different rate of FF occurrence are described in CF patients in Europe (France, Germany, Spain, etc.) but, at the moment, very little information are available from Italy. From 1/1/2007 to 30/09/2007, 35/220 (15.9%) of pts attending the CF Centre of Genova where colonized by filamentous fungi. The species distribution was: *A. fumigatus* (64%), *A. flavus* (25%), *S. apiospermum* (9%) others (2%).

R10 A PATIENT-ORIENTED LABORATORY MODEL FOR CYSTIC FIBROSIS (CF)

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The Department of Pathology and Laboratory Medicine of the Children's Hospital Bambino Gesù is developing a project of "clinicization" that is leading to the transition of the traditional concept of Department into an interdepartimental network. That implies the evolution of the academic definition of department towards a definition of "patient-centered" department.
A series of clinico-laboratory projects are being experienced, the prototype is the Cystic Fibrosis (CF) model.
In this model the patient represents the center of the CF universe, around which are rotating the pertinent and competent clinical units from one side and the CF Laboratory from the other side. Interaction and communication take place by a directional flow passing through the CF patient.
The CF Laboratory is innovative in that it carries out both clinical and laboratory work, either diagnostic or research.
The clinical activities consist in providing a qualified reception in a comfortable environment to patients and families by an informative and formative approach before performing the sweat test and a genetical counseling after the results of the various diagnostic tests.
To optimize the results the sweat test is carried out by experienced medical personnel and nurses.
The CF Lab consists of an integrated team from four specialized Labs: Molecular Genetics where gene mutations are searched, a specific Microbiology Lab for cultural and sensibility tests, a section of Chemical Chemistry for analytical determination and a dedicated histopathologist with special interest in CF.
Laboratory rounds and participation of Lab staff members into clinical grand rounds are promoting the clinical attitude of the participants, and are expected to contribute to the continuous improvement of the safety and quality care of CF patients.

R11 FROM RESEARCH TO CLINICAL PRACTICE. RCTs AND THEIR EXTERNAL VALIDITY

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Patient care and outcomes could be improved if the knowledge from research was better translated into practice. It has been estimated that 30–40% of patients do not receive treatments of proven effectiveness, whereas 20–25% receive treatments that are unnecessary or potentially harmful. This situation is in part due to two translational blocks that thwart the passage from basic research to clinical research, eg RCTs (type 1 translational block), and from clinical research and RCTs to clinical practice (type 2 translational block). Frequent information gaps due to inadequate external validity contribute substantially to the translational roadblock between RCTs and clinical practice (type 2 translational block). The external validity of an RCT regards the information needed to apply the trial results in the appropriate patients and settings, but it is often neglected, inadequate and unclear. Inclusion and exclusion criteria; ratio between randomized and eligible patients; heterogeneity, baseline risk and comorbidity of patients; selection of participating centres and researchers; rate and reasons of discontinuation: this is an incomplete list of the major requirements of external validity. When the information on these (and other) areas is inadequate or unclear, clinicians' uncertainty and underuse or even misuse of treatments are the consequences. The conclusions are that:
Trialists should pay to the external validity the same attention and completeness of information they usually pay to the internal validity. Pre-established subgroup analyses in megatrials implying patients' heterogeneity (eg, due to comorbidity) could be of use to guide the trial application in practice.
Clinicians should take into account the limitations of the RCTs before applying their results, perhaps using guidelines assembling the full evidence available in order to compensate the lack of information of the individual RCT of interest.

R12 EVIDENCE BASED MEDICINE – ONE AID IN PROVIDING GOOD CF CARE

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The survival of people with cystic fibrosis has steadily improved over the years due to increasingly effective nutritional and antibiotic treatment for the secondary effects of the basic defect. The care the patient receives from an early age is the main determinant of health, quality of life and length of survival; but numerous studies show major differences between CF Centres reflecting different patterns of care. The features of early management later associated with better lung function include early diagnosis by screening, lack of symptoms and higher weight for age at diagnosis, more clinic visits, respiratory cultures, intravenous antibiotics, corticosteroids and mucolytics.
An information revolution has taken place over the past 10–15 years including the growth of Evidence Based Medicine defined as "the conscientious explicit and judicious use of current best evidence in making decisions about care of individual patients". There are now Systematic Reviews by the Cochrane Collaboration on more than 40 areas of treatment for CF and more in preparation. These make a variable contribution to CF care but are often more a statistical analysis of the methodology of the published trials rather than a practical help to the clinician – most call for further randomized controlled trials. Although a useful record of published work, lack of large randomized controlled trials on some areas of treatment where benefit is nevertheless quite obvious to the experienced clinician, may delay by years the introduction of treatments later proved to be very effective e.g. the early eradication treatment of *Pseudomonas aeruginosa.*
So although Evidence Based Medicine has made and continues to make a significant contribution to CF care, it should be regarded as but one aid to better CF care – one additional aid to the expertise of experienced staff at CF Centres; expertise that has been acquired over many years of treating people with CF.

R13 A NEW MODEL OF CF DISEASE: NO F508, NO KINASE?

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Protein kinase CK2 is an essential heterodimer ($\alpha 2\beta 2$) whose constitutive activity controls inflammation, cancer and infection; unexplained hallmarks of CF disease. The deletion of only one amino acid (F, phenylalanine 508) causes most cystic fibrosis (CF) and our data connects this F508-CFTR region with a malfunctioning protein kinase binding site and suggest that ΔF508 induces a kinase-opathy. We noticed immediately C terminal to F508 lies a potential CK2 consensus motif ($F_{508}GVS_{511}YDE$; target serine, S, plus locating motif DE) and tested the idea that F508 is needed for CK2 function towards CFTR and *vice versa*.
Methods: Treharne et al *J Biol Chem* 2007 & *Am J Physiol* 1994 using models of CFTR/CK2 function (confocal, oocytes, single channel CFTR kinetics) coupled to CK2 assay in apical membrane samples and WT (HBE) and homozygous ΔF508 (CFBE) cell lines.
Results: Compared to HBE membranes containing WT-CFTR, CFBE membrane blots contain no detectable catalytic CK2α, CK2β, unaffected) without affecting PKA/PKC. Thus membrane local CK2 is absent in CF (confirmed by activity assay). Further, unlike in wild-type nasal epithelial biopsies, those from ΔF508 CF patients do not localise CK2α to the apical membrane (n>3). In oocytes co-expressing human WT CFTR with human CK2, CFTR (but not ΔF508-CFTR) closes by